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Award Number: W81XWH-10-1-0127

TITLE: Columbia SMA Project: A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)

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REPORT DATE: June 2012

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
June 2012	Annual	3 May 2011 – 2 May 2012

4. TITLE AND SUBTITLE

Columbia SMA Project: A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0127

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Columbia University
New York, NY 10032

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This three-year randomized controlled trial is designed to assess the effectiveness of a comprehensive regimen incorporating strengthening and aerobic exercise in 14 ambulatory patients with spinal muscular atrophy (SMA). To date, 22 subjects have been screened and 10 subjects enrolled. Reasons for non-participation were most often cost and burden of travel. Protocol adherence has been outstanding thus far with only one deviation with regards to visit schedule. All testing and intervention procedures have been well tolerated. All non-serious adverse events are closely monitored by an independent safety monitor who has approved continuation of the study without modification thus far. The overall goal of this project is to provide novel insights into the effectiveness of aerobic and strengthening exercise to improve function in SMA, and explore the physiology underlying its effects.

15. SUBJECT TERMS
Spinal Muscular Atrophy, Exercise, Ambulatory, Clinical Trial

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	48	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION: This three-year randomized controlled trial is designed to assess the effectiveness of a comprehensive regimen incorporating strengthening and aerobic exercise in 14 ambulatory patients with spinal muscular atrophy (SMA). SMA causes significant disability, and there is no effective drug treatment. Maximizing function, endurance, general health and well being, in an effort to modulate disease morbidity is the focus of supportive treatment modalities. There are no controlled data evaluating the role of exercise in SMA. Several controlled animal studies provide compelling evidence for benefit from exercise. The overall goal of this project is to provide novel insights into the effectiveness of aerobic and strengthening exercise to improve function in SMA, and explore the physiology underlying its effects. Moreover, by studying the effects of exercise in human patients, we hope to provide the first application of these studies for improved standard of care.

BODY: This report reflects the past two years of work on this project. The first year of this project consisted of mainly start-up and administrative procedures. For administrative and IRB reasons our proposed timeline was delayed nearly 2 months. Definitive IRB approvals were obtained from both Columbia University and the USAMRMC ORP HRPO and the first subject was enrolled on December 17, 2010. Since, 22 subjects have been screened all of which met eligibility requirements for participation. Of those, 12 chose not to participate. Reasons for non-participation were most often cost and burden of travel. To date, all 10 subjects have been randomized, are actively participating, and study procedures are on-going. Below is a summary of the progress thus far outlined by the specific aims of the project.

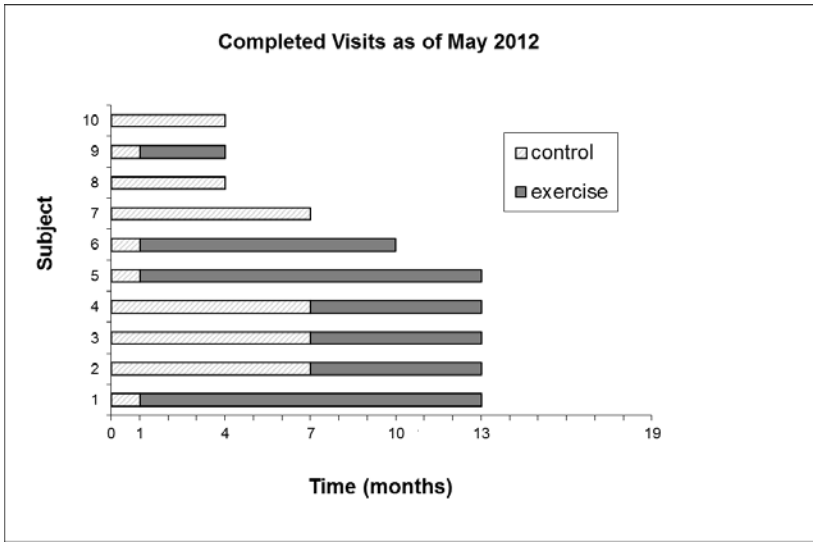
Aim 1: To assess the effect of comprehensive strengthening and aerobic exercise on clinical measures of function in patients with SMA.

Hypothesis 1: A comprehensive strengthening and aerobic exercise regimen will improve performance by ambulatory subjects with SMA on measures of clinical function, including the six-minute walk test (6MWT), Hammersmith motor function scale, expanded (HMFSE), 10 meter walk/run test and kinematic parameters of gait.

Significance: There are at present no studies that detail the effectiveness of exercise in modulating clinical function in SMA. Demonstration of such benefit is expected to have immediate impact on the management of the disease.

The 10 subjects enrolled thus far are actively continuing with their study participation and have been randomized following their baseline visit as per protocol. Figure 1 below outlines the status of each subject enrolled to date. Six subjects were randomized to the control group and 4 to the intervention arm of the study. All 10 have completed their baseline and month 1 visits, 7 subjects have completed their month 7 visit, 6 subjects have completed their month 10 visit, and 5 subjects have completed their month 13 visit. The first subject enrolled is due to complete his participation this June.

Figure 1. Enrollment status by subject



Subject baseline characteristics as well as clinical measures are included in Table 1 below. All clinical assessments were performed by our blinded physical therapist evaluator. Of the 10 subjects 3 are 18 years of age or younger. All ten subjects have impaired function as demonstrated on the functional scales included in the Table below (6MWT, HFMSE, 10 meter walk/run, and TUG). Exercise tolerance (VO2 max) was also impaired in all subjects and is described in more detail under Aim2 below. As expected in ambulatory SMA, pulmonary function is within normal limits for all of the 10 participants.

Table 1. Baseline characteristics of study subjects.

Variable	Mean (SD)	Range
Age (years)	32.7 (14.9)	10.0 – 48
Age at symptom onset (years)	9.5 (5.9)	1.0 – 19
Gender (% male)	70%	
Six Minute Walk Test (6MWT) Distance (meters)	332.3 (113.8)	117 – 498
Hammersmith Functional Motor Scale, Expanded (HFMSE)	51.5 (6.9)	44 – 63
10 meter walk/run (seconds)	8.26 (3.06)	5.2 – 13.18
Timed Up and Go Test (TUG) (seconds)	15.81 (10.74)	5.27 – 41.11
Forced Vital Capacity (FVC) (% predicted)	102.3 (13.8)	83 – 124
VO2 Max (% predicted)	34.23 (11.0)	18.7 – 57.0

In addition to the above referenced assessments, we have collected standardized quality of life assessments (Peds QoL and SF-36) and subjective measures of perceived fatigue (Fatigue Severity Scale and Pediatric Multidimensional Fatigue Scale) at all clinic visits. Habitual physical activity levels using the ActiGraph accelerometers over a 7 consecutive day period during each 3 month study segment has also been collected in all 10 subjects. Both measures provide descriptive and quantitative information on fatigue and daily activity for which we can explore the possible responses to the intervention during data analysis at the end of the study.

Adherence to the protocol has been excellent to date. There have been 12 protocol deviations where subject visits were performed out of window due to scheduling conflicts. The average number of days out of window for these 12 visits was 6.7 days with a range from 1 – 14 days. The 10 enrolled subjects have completed all assessments and outcome measures at each visit as described in the protocol in the order described in the protocol. There have been no missed outcome measures or deviations from this in-clinic visit protocol

We have incorporated several different assessments to measure participant compliance to the exercise intervention including, exercise diaries, heart rate monitors, as well as scheduled and frequent correspondence with the study team. In general, participant compliance with the prescription seems excellent based on interim Skype calls and in-clinic study visits. At study completion, quantitative analysis of our compliance measures will be performed. For the 4 subjects enrolled in the intervention arm of the study and the 4 in the open-label exercise period, individualized exercise programs have been developed which include both the aerobic or cycling component and the strengthening component.

As outlined in the protocol, the initial design of the exercise regimen is structured based on performance on the exercise tolerance test as well as strength assessments collected by the blinded evaluator. As anticipated, none of the subjects were able to cycle continuously for 30 minutes at study start. As such, their programs were tailored and adjusted according to their ability. All 8 exercising participants have safely made incremental and steady progress in cycling time and tolerance. Notably, of the 6 subjects who have been exercising for 6 months or longer, 3 individuals are now able to cycle for 30 minutes continuously 5 times per week. As planned, video-conferencing visits using Skype have been implemented to ensure the subjects are performing the exercise correctly, change or advance their program, and to enhance exercise safety and adherence. During these visits, interim medical histories, concomitant medications and adverse events are also collected. Subjects enrolled in the control arm of the study also participate in the video-conferencing visits on a similar schedule.

Overall, the exercise intervention, both cycling and strengthening components, have been safe and well tolerated. With the exception of one serious event un-related to the study, adverse events reported have been mild or moderate using the CTCAE Adverse Event Classification System. Falls are a clinically important problem in people with weakness (Rubenstein LZ 2002) and neuromuscular disease (Pieterse AJ, 2006) and are the most commonly reported adverse event in this study thus far with 116 reports of falls in 10 subjects over 85 total months of study participation. There has been no notable change (increase) in fall frequency of any subject while in the exercise arm. Muscle soreness and fatigue were also reported but much less frequently in both control and exercise subjects. Monthly reports have been reviewed by Dr. Nancy Strauss, our independent un-blinded safety monitor, who has approved continuing this study without modification (see attached Appendix 1).

Aim 2: To explore the effect of a sustained exercise regimen on exercise capacity in patients with SMA.

Hypothesis 2: A comprehensive, intensive and sustained strengthening and aerobic exercise regimen will improve exercise capacity as measured by maximum oxygen uptake (VO_2 max), as well as maximal work capacity (Wmax) in patients with SMA

Significance: There is no literature addressing the role of a comprehensive exercise program on exercise capacity, or the relationship of exercise capacity with established clinical measures, in SMA.

Because maximal exercise testing including measurement of maximal oxygen uptake and work has not been administered previously to persons with SMA, the feasibility was not fully known at the start of the study. To date all 10 subjects enrolled have successfully performed one or more maximal exercise tests without adverse sequellae (Performance at baseline for all subjects is described in this report.

Exercise tolerance is determined by the functioning of multiple body systems including the cardiovascular, respiratory, and neuromuscular systems. A limitation in one or more body systems will result in reduced exercise capacity or tolerance. The variables demonstrating exercise tolerance, and hence the feasibility of the test include the respiratory exchange ratio (RER), ratings of perceived exertion (RPE), maximal oxygen uptake (VO2max), maximal heart rate (HRmax), and the reason for test termination. The RER represents the ratio of carbon dioxide produced to the oxygen uptake, and is an indicator of the adequacy of individual efforts to attain their maximal capacity. An RER greater than 1 is a standard criterion used to indicate the attainment of maximal tolerance (capacity). In healthy persons, the cardiorespiratory system is the limiting factor for exercise and an RER >1 will occur once the capacity of the cardiorespiratory system has been reached. Individuals who have significant respiratory, neuromuscular, or orthopedic limitations would not be expected to attain an RER > 1, because these would reach their maximal capacity earlier due to the limitations imposed by these systems or physical limitations. Another criterion for maximal exercise tolerance is voluntary fatigue, which is usually defined as an RPE greater than 8 out of 10 points (hard to extremely hard) on the OMNI Scale, a 10 point scale indicating '1' as extremely easy to '10' as extremely hard. The results of the exercise tests at baseline in all 10 subjects are shown in Table 2 below.

Table 2. Exercise Tolerance Test Baseline Results

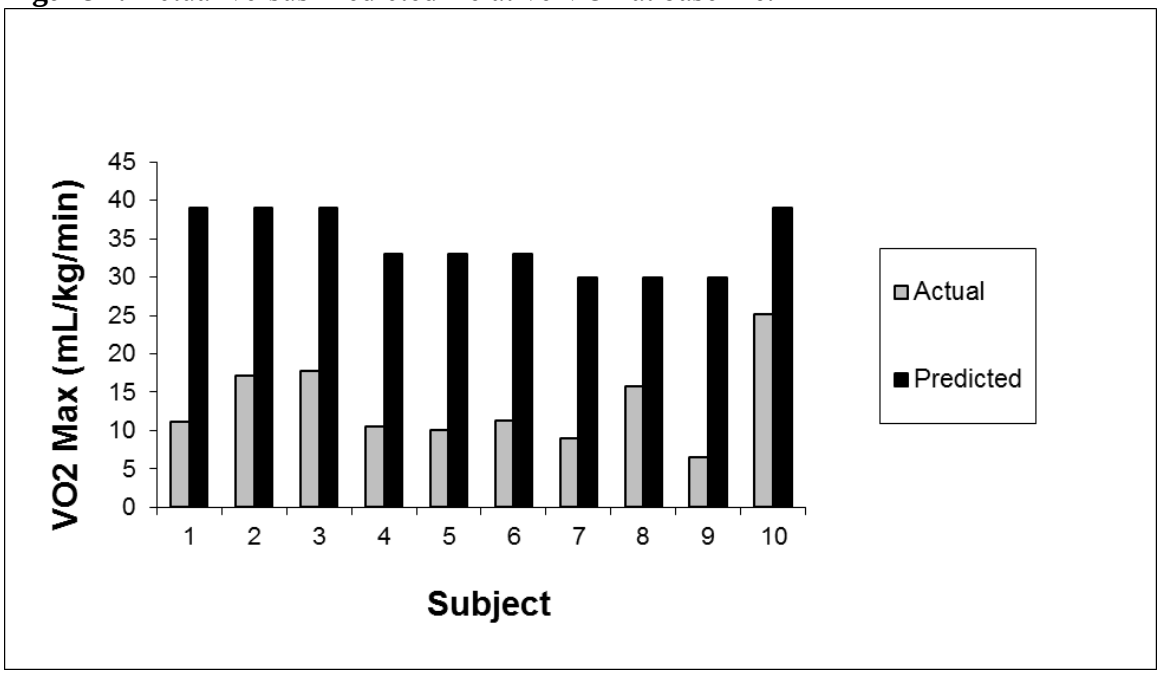
Subject	RER	RPE	Explanation
1	1.37	9	could not maintain pedal speed
2	1.08	10	RER >1.1, RPE 10
3	0.88	9	Pt request, knee pain
4	0.85	8	Fatigue and subject could not maintain pedal speed
5	1.05	10	Fatigue, RPE >/+9
6	0.93	8	Fatigue, leg discomfort, could not maintain pedal speed
7	1.15	10	Fatigue, subject requested to stop, could not maintain pedal speed
8	1.02	6	Fatigue, could not maintain pedal speed
9	0.86	8	Pt request, knee pain
10	1.08	10	Fatigue, could not maintain pedal speed

*RER = Respiratory Exchange Ratio*RPE = Rate of Perceived Exertion

All but one of the subjects reached an RPE of 8 -10, indicating they were working hard to extremely hard at the end of exercise. Tests were terminated due to fatigue in all but one subject, who stopped due to knee pain, related to internal rotation of the lower extremities and inherent muscle weakness associated with SMA. Further supporting the attainment of maximal exercise tolerance or capacity, 6 of the 10 subjects reached RER greater than 1, indicating that these subject's neuromuscular disease did not exert a substantial limitation upon their exercise capacity. In the case of the remaining four subjects who did not attain an RER of 1, two stopped due to knee pain and the other two due to lower extremity fatigue., Fatigue is a normal response to maximal exercise test, and normal fatigue resolves within a few minutes of ceasing exercise, although some fatigue often persists throughout the day, but does not interfere with usual daily activities. With rest all of the subjects were able to walk to their cars following the test, and none reported inability to engage in their activities of daily living. It should be noted, however that the exercise tolerance test was administered following many tests performed throughout the study visit. So, it is difficult to fully distinguish the contributory factors to the fatigue.

In evaluating the maximal exercise tolerance of our subjects, we compared their measured VO2max to the predicted values for healthy individuals of the same sex and age. Figure 1 below shows the subjects' actual VO2 max and predicted VO2max, presented relative to body mass (mL/kg/min) to standardize for body size effects on oxygen uptake (i.e., larger individuals will have higher absolute oxygen uptake than smaller individuals). As can be seen in Figure 2 below, the subjects' actual VO2max is substantially lower than predicted, and likely reflects the effects of deconditioning resulting from limited engagement in physical activity secondary to physical function limitations associated with SMA. This is supported by data in other neurological diseases such as Parkinson's Disease and Multiple Sclerosis which have shown concurrently decreased VO2max and low levels of physical activity (Mostert & Kesselring, 2002; Garber et al, 2003).

Figure 2. Actual versus Predicted Relative VO2 at baseline.



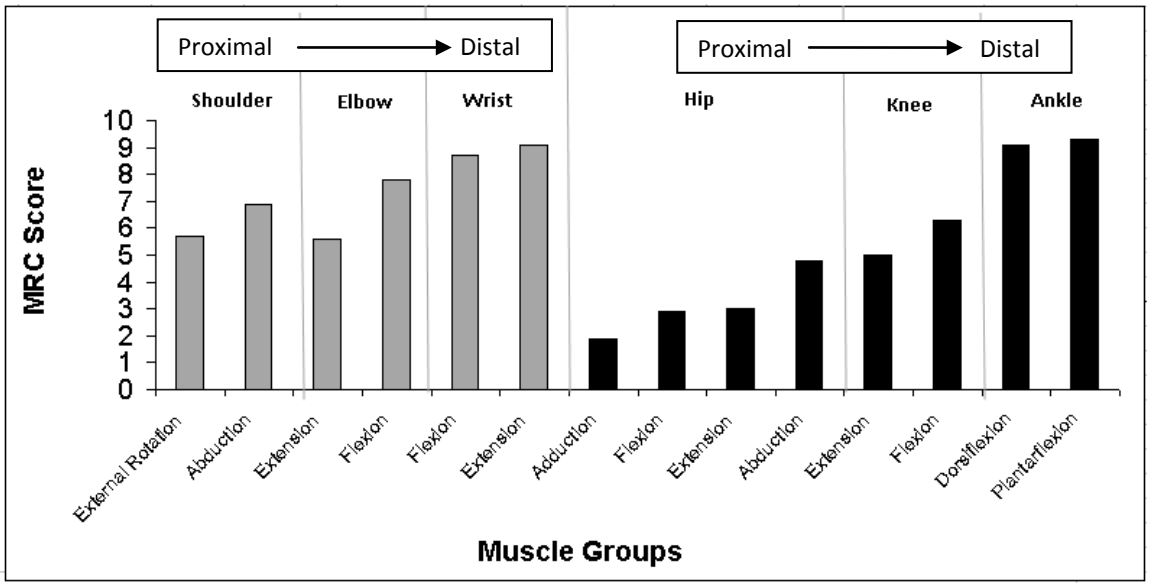
Aim 3: To assess the effect of comprehensive strengthening and aerobic exercise on muscle strength measures in patients with SMA.

Hypothesis 1: A comprehensive strengthening and aerobic exercise regimen will improve measures of muscle strength using manual muscle testing (MMT) augmented by hand-held dynamometry (HHD).

Significance: There is at this time little evidence describing the effect of exercise on muscle strength in SMA, and the relationship between such effect and measures of clinical function. Demonstration of such benefit is expected to have immediate impact on the management of the disease.

Manual muscle testing (MMT) is performed as part of a routine neurological exam. Manual muscle testing (MMT) was found to be feasible in children with SMA and was sensitive enough to detect relative differences between different muscles (Carter 1995, Deymeer 1997, Wang HY 2002). Below are the average MMT scores at baseline for all 10 subjects by muscle groups of the arms and legs (Figure 3). As expected and highlighted in the graph below, there is a clear centripetal pattern of weakness with proximal musculature more affected than distal musculature. Using MMT and this known, clearly defined pattern of weakness, the responsiveness of these muscles to treatment can be explored as a whole as well as the individual selective muscle groups.

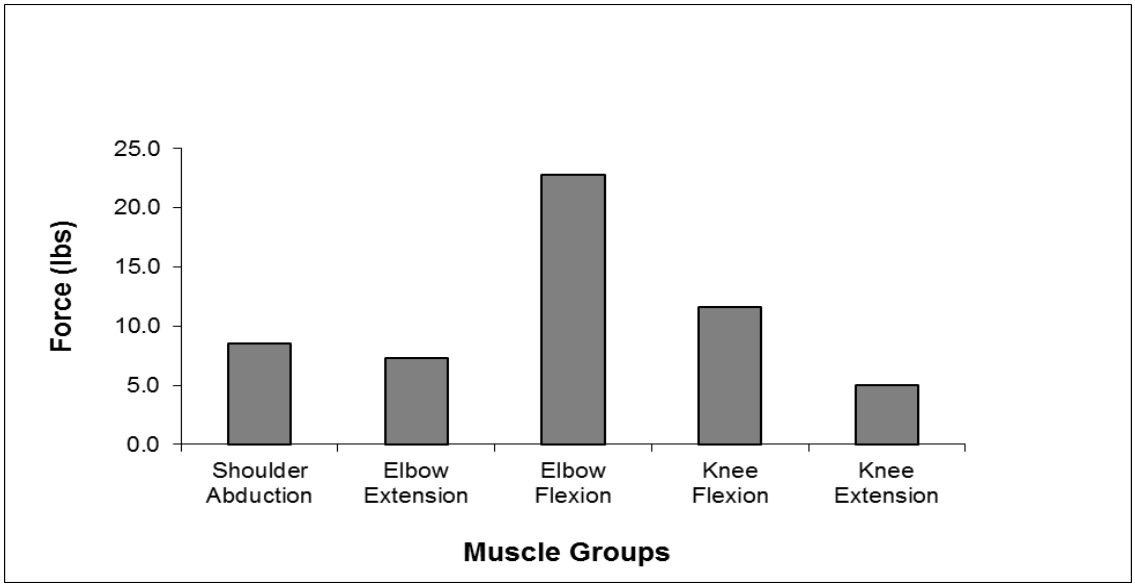
Figure 3. Average Manual Muscle Test (MMT) using the Medical Research Council (MRC) grading scale for each muscle group at baseline.



Research has shown MMT lacks sensitivity in detecting weakness, particularly in less affected or muscles with strength in normal ranges (Bohannon 2005). As such, the addition of hand-held dynamometry (HHD) has been shown to increase the sensitivity of MMT in SMA children aged 5 years or older with good inter-rater reliability and reproducibility for some leg muscle groups (Merlini 2002). Of the leg muscles tested only knee extensors and flexors performed reliably. Using HHD, knee extensors in SMA patients were weaker than flexors which in contrast to stronger knee extensors in the healthy population (Beenakker E 2001).

Below are the average HHD scores at baseline for each subject by muscle group (Figure 4). Together MMT, augmented by HHD, will provide a comprehensive evaluation of the participant's muscle strength and responsiveness to the exercise intervention. With this prospective detailed examination, the relationship of muscle strength to walking performance and responsiveness to exercise treatment can be explored.

Figure 4. Average strength scores using hand held dynamometry (HHD) for each muscle group at baseline.



KEY RESEARCH ACCOMPLISHMENTS: This report reflects the work done in first 2 years of the project. While the majority of the first year was devoted to start-up and administrative activities, the past year has been devoted to recruitment and study procedures. Our key accomplishments are outlined below:

- To date 10 of the 14 proposed subjects have been enrolled and randomized. Adherence to the protocol is excellent. The 10 enrolled subjects have completed all assessments and outcome measures at each visit as described in the protocol. Subject retention is also excellent with no missed in-clinic study visits to date.

- As a recruitment strategy, we have allocated additional resources to support travel for participants for in-clinic study visits living greater than 100 miles away. To date, study inquiries largely come from internet resources (ie. clinical trials.gov) and a good portion of eligible candidates live outside of the Greater New York area. Providing a patient allowance which facilitates travel from distances outside our region makes participation feasible for some patients.

- Data management is on-going and we continue to develop our study database with the many clinical and physiologic measures as part of the study. From this rich database, 4 meeting abstracts (described below) have already been written and will be presented on baseline measurements. These analyses provide useful information to the field on new outcome measures and clinical phenomenon not yet explored in the ambulatory SMA population.

REPORTABLE OUTCOMES: An abstract entitled "Falls and Spinal Muscular Atrophy (SMA): Exploring Cause and Prevention" was presented at the American Academy of Neurology 64th Annual Meeting, April 21 to April 28, in New Orleans, LA.

Additionally, the following abstracts will be presented at International SMA Research Group Meeting, Families of SMA Annual Conference, June 21 – 23, 2012, Bloomington, MN.

- Performance of the Timed "Up & Go" Test (TUG) in Spinal Muscular Atrophy (SMA)
- Spinal Muscular Atrophy (SMA): An Asymmetric Disease by Patient Report
- Leg Strength Predicts Dysfunction and Fatigue in Ambulatory Spinal Muscular Atrophy (SMA)

These abstracts are a product of the baseline characteristics and data collected on the 10 subjects enrolled to date. The full abstracts for all 4 presentations are included in the Appendix (2).

CONCLUSION: This report summarizes the first two year of a three-year project. In addition to successfully obtaining IRB approvals and completing all relevant study start up procedures, 10 of the 14 planned subjects have been enrolled and randomized and the first enrolled subjects will complete the study this summer. Protocol adherence has been outstanding thus far with only one deviation with regards to visit schedule. All testing and intervention procedures have been well tolerated without any serious adverse events and all non-serious adverse events are closely monitored by an independent safety monitor who has approved continuation of the study without modification thus far. We continue to explore alternative recruitment strategies to enroll the last four planned subjects.

SO WHAT SECTION: The result of this prospective, single (examiner) blinded, randomized and controlled clinical trial of the effect of exercise on an established functional outcome measure will have immediate impact on clinical practice by providing important guidance to clinical management of SMA patients. The effect of exercise on additional clinical measures as well as on formal exercise performance will provide mechanistic information on the changes underlying any observed improvement in exercise performance. These results would also inform our understanding of the mechanisms underlying weakness and fatigue in SMA.

To our knowledge, this will be the first randomized, controlled clinical trial of exercise in SMA. Even if we do not succeed in establishing the effectiveness of this intervention, this study will establish the safety of exercise in SMA. This study offers an assessment of the potential complications of a comprehensive exercise program in SMA, it will advise and inform future clinical practice by confirming or questioning the current treatment paradigm.

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Columbia SMA Project: A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)

PI: Darryl C. De Vivo, MD

Adverse Event Summary Report By Subject

Reporting period: December 1, 2010 thru April 30, 2012

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Pre-assignment	Pulmo/ Upper Resp	URI / fever	O	Month 1	1/7/2011	12/27/2010	1/12/2011	RC	0	1	No
001	Pre-assignment	Musculo/ Skeletal	Muscle soreness	O	Month 1	1/14/2011	12/18/2010	12/21/2010	RC	2	1	No
001	Pre-assignment	Consti	Fatigue	M	Month 1	1/14/2011	12/18/2010	12/19/2010	RC	2	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	12/20/2010	12/20/2010	RC	0	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	1/6/2011	1/6/2011	RC	0	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	1/8/2011	1/8/2011	RC	0	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	1/10/2011	1/10/2011	RC	0	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 1	1/19/2011	1/19/2011	1/19/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Muscle soreness	O	TC week 5	1/21/2011	1/14/2011	1/17/2011	RC	2	1	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 6	1/28/2011	1/22/2011	1/22/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	M	TC week 6	1/28/2011	1/22/2011	2/4/2011	RC	1	2	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 7	2/4/2011	1/28/2011	1/28/2011	RC	1	0	No
001	Exercise	Neurol	Paraesthesias right shoulder	M	TC week 7	2/4/2011	1/31/2011		CO	1	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)

[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)

[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)

[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 7	2/6/2011	2/4/2011	2/17/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 8	2/11/2011	2/7/2011	2/7/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	O	TC week 11	3/4/2011	2/24/2011	2/24/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Low back pain	O	TC week 13	3/18/2011	2/26/2011	2/26/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Fall	O	TC week 13	3/18/2011	3/7/2011	3/7/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 15	4/1/2011	4/1/2011	4/1/2011	RC	1	0	No
001	Exercise	Gastro-intestinal	Diarrhea	M	TC week 15	4/1/2011	3/31/2011	4/7/2011	RC	0	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	O	Month 4	4/8/2011	4/6/2011	4/7/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Neck /shoulder pain	M	TC week 18	4/22/2011	4/15/2011	5/12/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	M	TC week 18	4/22/2011	4/15/2011		CO	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	O	TC week 20	5/6/2011	5/2/2011	5/3/2011	RC	1	1	No

1 Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
2 Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
3 PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
4 Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 20	5/6/2011	5/4/2011	5/4/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Hip pain	M	TC week 22	5/20/2011	5/15/2011		CO	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 22	5/202011	5/16/2011	5/16/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 24	6/3/2011	6/1/2011	6/1/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 25	6/10/2011	6/7/2011	6/7/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 25	6/10/2011	6/8/2011	6/8/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	O	TC week 25	6/10/2011	6/9/2011	6/13/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Fall	O	Month 7	7/1/2011	6/23/2011	7/2/2011	RC	1	1	No
001	Exercise	Gastro-intestinal	Constipation	M	Month 7	7/1/2011	6/15/2011	7/5/2011	RC	0	1	No
001	Exercise	Constitutional	Fatigue	M	Month 7	7/1/2011	6/29/2011	6/30/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 30	7/15/2011	7/6/2011	7/6/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 30	7/15/2011	7/13/2011	7/13/2011	RC	1	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Exercise	Musculo/ Skeletal	Falls	M	TC week 30	7/15/2011	7/14/2011	7/15/2011	RC	0	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 33	8/5/2011	8/1/2011	8/1/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 33	8/5/2011	8/3/2011	8/3/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 35	8/18/2011	8/13/2011	8/13/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 35	8/18/2011	8/16/2011	8/16/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 37	9/26/2011	8/29/2011	8/29/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC Week 38	9/26/2011	9/4/2011	9/4/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC Week 40	9/26/2011	9/23/2011	9/23/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC Week 42	10/6/2011	10/3/11	10/3/11	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Muscle soreness (motor vehicle accident)	O	TC Week 46	11/2/2011	10/30/2011	11/11/2011	RC	0	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC Week 45	11/11/2011	10/29/2011	10/29/2011	RC	1	0	No

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[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Exercise	Musculo/ Skeletal	Fall	M	TC Week 47	11/11/2011	11/10/2011	11/10/2011	RC	1	0	No
001	Exercise	Lymph	Swollen lymph nodes	O	Month 13	1/4/2012	11/1/2011	11/28/2011	RC	0	0	No
001	Exercise	Infec.	Muscle aches/ fever	M	Month 13	1/4/2012	12/15/2011	12/17/2011	RC	0	0	No
001	Exercise	Pulmon/ Upper Resp.	Upper resp. infection	M	Month 13	1/4/2012	12/30/2011		CO	0	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	12/1/2011	12/1/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	12/30/2011	12/30/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	11/15/2011	11/15/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	12/14/2011	12/14/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	11/26/2011	11/26/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	11/27/2011	11/27/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	12/25/2011	12/25/2011	RC	1	0	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	12/7/2011	12/7/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/4/2012	12/31/2011	12/31/2011	RC	1	0	No
001	Exercise	Gastro	Gastroenteritis	O	TC month 15	3/7/2012	2/15/12	2/16/12	RC	0	1	No
001	Exercise	Infec	CMV infection	S	TC month 15	3/7/2012	2/20/2012	2/23/2012	RC	0	2	Yes
002	Pre-assignment	Pulmo/ Upper Resp	Cough / nasal congestion	O	Month 1	2/7/2011	2/3/2011	2/11/2011	RC	0	1	No
002	Pre-assignment	Musculo/ Skeletal	Muscle soreness	O	Month 1	2/7/2011	2/6/2011	2/8/2011	RC	0	1	No
002	Control	Musculo/ Skeletal	Muscle soreness	O	TC week 7	2/28/2011	2/21/2011	2/22/2011	RC	0	1	No
002	Control	Musculo/ Skeletal	Muscle soreness	O	TC week 7	2/28/2011	2/27/2011	2/28/2011	RC	0	1	No
002	Control	Musculo/ Skeletal	Leg weakness/ fatigue	M	TC week 13	4/25/2011	4/1/2011		CO	0	0	No
002	Control	Musculo/ Skeletal	Fall (1)	M	TC week 13	4/25/2011	4/5/2011	4/5/2011	RC	0	0	No
002	Control	Musculo/ Skeletal	Fall (2)	M	TC week 13	4/25/2011	4/5/2011	4/5/2011	RC	0	0	No
002	Control	Musculo/ Skeletal	Fall	O	Month 4	5/4/2011	4/20/2011	4/24/2011	RC	0	1	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
002	Control	Musculo/ Skeletal	Fall	M	Month 4	5/4/2011	5/4/2011	5/4/2011	RC	1	0	No
002	Control	Musculo/ Skeletal	Muscle soreness	O	TC week 17	5/9/2011	5/5/2011	5/7/2011	RC	1	1	No
002	Control	Musculo/ Skeletal	Fall	M	TC week 24	6/27/2011	6/16/2011	6/16/2011	RC	0	0	No
002	Open-Label Exercise	Constitutional	Fatigue	M	TC week 31	8/15/2011	8/14/2011	8/15/2011	RC	0	0	No
002	Open-Label Exercise	Musculo/ Skeletal	Fall	M	TC week 32	8/22/2011	8/21/2011	8/21/2011	RC	1	0	No
002	Open-Label Exercise	Musculo/ Skeletal	Fall	M	TC week 32	8/22/2011	8/22/2011	8/22/2011	RC	1	0	No
002	Open-Label Exercise	Pulmo/ Upper Resp	Cough with some phlegm	M	TC week 36	9/12/2011	9/9/2011	9/12/2011	RC	0	0	No
002	Open-Label Exercise	Audito / Ear	Ear pain/infection	O	TC week 36	9/28/2011	9/26/2011	10/6/2011	CO	0	1	No
002	Open –Label Exercise	Musculo/ Skeletal	Leg weakness/ fatigue	M	TC week 36	9/28/2011	9/3/2011		CO	1	5	No
002	Open-Label Exercise	Musculo/ Skeletal	Fall	M	Month 10	10/27/2011	10/27/2011	10/27/2011	RC	1	0	No
002	Open-Label Exercise	Musculo/ Skeletal	Fall	M	Month 10	10/27/2011	10/27/2011	10/27/2011	RC	1	0	No

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2 Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
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4 Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
002	Open-Label Exercise	Musculo/ Skeletal	Fall	M	Month 13	1/26/2012	12/26/2012	12/26/2012	RC	1	0	No
002	Open-Label Exercise	Derm	Ingrown Toenail	O	Month 13	1/26/2012	1/10/2012	1/24/2012	RC	0	1,2	No
003	Pre-assignment	Neurological	Migraine headache	O	Month 1	3/10/2011	2/14/2011	2/14/2011	RC	0	1	No
003	Pre-assignment	Neurological	Migraine headache	O	Month 1	3/10/2011	3/7/2011	3/7/2011	RC	0	1	No
003	Control	Musculo/ Skeletal	Fall	M	TC week	3/15/2011	3/13/2011	3/13/2011	RC	0	0	No
003	Control	Neurological	Migraine headache	O	TC week 8	4/5/2011	4/4/2011	4/4/2011	RC	0	1	No
003	Control	Neurological	Migraine headache	O	TC week 11	5/3/2011	4/11/2011	4/11/2011	RC	0	1	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 11	5/3/2011	4/11/2011	4/11/2011	RC	0	0	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 11	5/3/2011	4/19/2011	4/19/2011	RC	0	0	No
003	Control	Neurological	Migraine headache	O	TC week 11	5/3/2011	4/21/2011	4/21/2011	RC	0	1	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 11	5/3/2011	4/23/2011	4/23/2011	RC	0	0	No

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[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
003	Control	Musculo/ Skeletal	Fall	M	TC week 11	5/3/2011	4/29/2011	4/29/2011	RC	0	0	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 11	5/3/2011	5/3/2011	5/3/2011	RC	0	0	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 15	5/24/2011	5/8/2011	5/8/2011	RC	0	0	No
003	Control	Neurological	Migraine headache	O	Month 4	6/10/2011	6/5/2011	6/5/2011	RC	0	1	No
003	Control	Neurological	Migraine headache	O	Month 4	6/10/2011	6/9/2011	6/9/2011	RC	0	1	No
003	Control	Neurological	Migraine headache	O	Month 7	8/19/2011	7/31/2011	8/1/2011	RC	0	1	No
003	Control	Neurological	Migraine headache	O	Month 7	8/19/2011	8/7/2011	8/7/2011	RC	0	1	No
003	Control	Musculo/ Skeletal	Falls	M	Month 7	8/19/2011	6/27/2011	8/12/2011	RC	0	0	No
003	Open-Label Exercise	Neurological	Migraine Headache	M	TC week 31	9/8/2011	9/2/2011	9/2/2011	RC	0	0	No
003	Open-Label Exercise	Neurological	Migraine Headache	O	TC week 31	9/8/2011	9/4/2011	9/4/2011	RC	0	1	No
003	Open-Label Exercise	Musculo/ Skeletal	Fall	M	TC week 33	9/23/2011	9/22/2011	9/22/2011	RC	0	0	No
003	Open-Label Exercise	Neurological	Migraine Headache	O	TC week 33	9/23/2011	9/23/2011	9/23/2011	RC	0	0	No
003	Open-Label Exercise	Neurological	Migraine Headache	O	TC week 34	9/28/2011	9/23/2011	9/23/2011	RC	0	1	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
003	Open-Label Exercise	Neurological	Migraine Headache	O	TC week 34	9/28/2011	9/25/2011	9/25/2011	RC	0	1	No
003	Open-Label Exercise	Pulmo/ Upper Resp	Strep throat	O	TC week 34	9/28/2011	9/26/2011	10/5/2011	RC	0	1	No
003	Open-Label Exercise	Neurological	Migraine headache	M	TC week 41	11/23/2011	10/24/2011	10/24/2011	RC	0	0	No
003	Open-Label Exercise	Neurological	Migraine Headache	O	TC Week 41	11/23/2011	11/10/2011	11/10/2011	RC	0	1	No
003	Open-Label Exercise	Neurological	Migraine Headache	O	TC Week 41	11/23/2011	11/18/2011	11/18/2011	RC	0	1	No
003	Open-Label Exercise	Pulmon/ Upper Resp.	Viral illness/ sore throat	O	TC Week 44	12/15/2011	12/7/2011	12/11/2011	RC	0	0	No
003	Open-Label Exercise	Musculo/ Skeletal	Fall	M	TC Week 44	12/15/2011	12/12/2011	12/12/2011	RC	1	0	No
003	Open-Label Exercise	Infec	Ear and sinus infection	O	Month 13	2/10/2012	1/16/2012	1/25/2012	RC	0	1	No
003	Open-Label Exercise	Musculo/ Skeletal	Fall	M	Month 13	2/10/2012	1/21/2012	1/21/2012	RC	1	0	No
003	Open-Label Exercise	Musculo/ Skeletal	Fall	M	Month 13	2/10/2012	1/21/2012	1/21/2012	RC	0	0	No
003	Open-Label Exercise	Neurological	Headache	O	Month 13	2/10/2012	1/21/2012	1/21/2012	RC	0	1	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
003	Open-Label Exercise	Neurological	Headache	O	Month 13	2/10/2012	1/31/2012	1/31/2012	RC	0	1	No
003	Open-Label Exercise	Pulmon/Upper Resp.	Common cold	M	Month 13	2/10/2012	1/9/2012	1/15/2012	RC	0	0	No
003	Open-Label Exercise	Audito/ Ear	Earache	M	Month 13	2/10/2012	1/15/2012	1/15/2012	RC	0	1	No
003	Open-Label Exercise	Musculo/ skeletal	L leg pain	M	TC Month 14	3/27/2012	3/21/2012		CO	0	0	No
004	Pre-assignment	Ocular/ Visual	Sty right eye	M	Month 1	4/1/2011	3/25/2011	4/3/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall (1)	M	Month 1	4/1/2011	3/12/2011	3/12/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall (2)	M	Month 1	4/1/2011	3/12/2011	3/12/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	4/1/2011	3/21/2011	3/21/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	4/1/2011	3/27/2011	3/27/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	TC week 7	4/20/2011	4/8/2011	4/8/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	TC week 7	4/20/2011	4/15/2011	4/15/2011	RC	0	0	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
004	Control	Musculo/ Skeletal	Fall	M	TC week7	4/20/2011	4/18/2011	4/18/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/2/2011	7/2/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/2/2011	7/2/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/3/2011	7/3/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/9/2011	7/9/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/24/2011	7/24/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/24/2011	7/24/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	7/25/2011	7/25/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	9/6/2011	9/6/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	8/10/2011	8/10/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	9/9/2011	9/9/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	Month 7	9/16/2011	9/10/2011	9/10/2011	RC	0	0	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
004	Open Label Exercise	Musculo/ Skeletal	Fall	M	TC week 31	10/3/2011	9/19/2011	9/19/2011	RC	0	0	No
004	Open Label Exercise	Musculo/ Skeletal	Muscle soreness	M	TC week 31	10/3/2011	10/3/2011	10/6/2011	RC	2	0	No
004	Open Label Exercise	Musculo/ Skeletal	Fall	M	Month 10	12/8/2011	10/21/2011	10/21/2011	RC	1	0	No
004	Open Label Exercise	Musculo/ Skeletal	Muscle soreness	M	Month 10	12/9/2011	10/26/2011	10/26/2011	RC	1	0	No
004	Open Label Exercise	Musculo/ Skeletal	Fall	M	Month 10	12/9/2011	11/12/2011	11/12/2011	RC	1	0	No
004	Open Label Exercise	Musculo/ Skeletal	Fall	M	Month 10	12/9/2011	11/24/2011	11/24/2011	RC	1	0	No
004	Open Label Exercise	Musculo/ skeletal	Fall	M	Month 13	3/8/2012	12/9/2012	12/9/2012	RC	1	0	No
004	Open Label Exercise	Musculo/ skeletal	Fall	M	Month 13	3/8/2012	12/10/2012	12/10/2012	RC	1	0	No
004	Open Label Exercise	Musculo/ skeletal	Fall	M	Month 13	3/8/2012	1/15/2012	1/15/2012	RC	1	0	No
004	Open Label Exercise	Pulmon/ upper resp	Common cold	M	Month 13	3/8/2012	1/31/2012	2/2/2012	RC	1	0	No
004	Open label exercise	Musculo/ skeletal	Soreness	M	Month 13	3/8/2012	2/4/2012	2/4/2012	RC	1	0	No
004	Open label exercise	Musculo/skeletal	Fall	M	Month 13	3/8/2012	2/12/2012	2/12/2012	RC	1	0	No

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Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
004	Open label exercise	Musculo/ skeletal	Fall	M	Month 13	3/8/2012	2/23/2012	2/23/2012	RC	1	0	No
004	Open label exercise	Musculo/ skeletal	Fall	M	Month 13	3/8/2012	2/26/2012	2/26/2012	RC	1	0	No
004	Open label exercise	Musculo/skeletal	Fall	M	Month 13	3/8/2012	3/3/2012	3/3/2012	RC	1	0	No
005	Pre-assignment	ENT / Upper Resp	Sore throat / URI	M	Month 1	5/2/2011	4/20/2011	4/21/2011	RC	0	0	No
005	Exercise	Musculo/ Skeletal	Muscle soreness	M	TC week 5	5/9/2011	5/7/2011	5/8/2011	RC	2	0	No
005	Exercise	ENT / Upper Resp	Nasal congestion	M	TC week 6	5/16/2011	5/15/2011	5/23/2011	RC	0	0	No
005	Exercise	Musculo/ Skeletal	Muscle soreness	M	TC week 6	5/16/2011	5/15/2011	5/16/2011	RC	2	0	No
005	Exercise	Musculo/ Skeletal	Fall	M	Month 4	7/18/2011	7/14/2011	7/14/2011	RC	1	0	No
005	Exercise	Musculo/ Skeletal	Fall	M	TC week 20	8/22/2011	8/21/2011	8/21/2011	RC	1	0	No
005	Exercise	Constitutional	General malaise	M	Month 7	10/20/2011	9/1/2011	9/15/2011	RC	1	0	No
005	Exercise	Musculo/ Skeletal	Low back/ left hip pain	M	TC week 31	11/23/2011	11/21/2011	12/6/2011	RC	1	0	No
005	Exercise	Musculo/ Skeletal	Mild pain L buttocks, posterior hip	O	Month 10	12/9/2011	12/8/2011	12/29/2011	RC	1	1	No
005	Exercise	Musculo/ Skeletal	Fall	M	TC Week 42	1/10/2012	12/20/2011	12/20/2011	RC	1	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
005	Exercise	Musculo/ Skeletal	Fall	O	TC Week 42	1/10/2012	1/6/2012	1/6/2012	RC	0	1	No
005	Exercise	Musculo/ skeletal	L hip pain	O	TC week 47	2/17/2012	2/10/2012	4/13/2012	RC	1	1	No
005	Exercise	Musculo/ Skeletal	Fall and increased soreness	M	week 55	4/16/2012	4/13/2012	4/30/2012	RC	1	0	No
005	Exercise	Musculo/ Skeletal	Fall	M	week 56	4/25/2012	4/20/2012	4/20/12	RC	1	0	No
006	Exercise	ENT	Sore throat	O	TC week 26	1/4/2012	1/3/2012	1/14/2012	CO	0	1	No
007	Control	Constitutional	Generalized fatigue and weakness	M	Month 1	10/7/2011	9/14/2011	9/19/2011	RC	0	0	No
007	Control	Musculo/ Skeletal	Fall	M	Month 3	11/17/2011	11/10/2011	11/10/2011	RC	0	0	No
007	Control	Musculo/ Skeletal	Fall	M	Month 6	2/24/2012	1/13/12	1/13/12	RC	0	0	No
007	Control	Musculo/ Skeletal	Fall	M	Month 6	2/24/2012	1/31/2012	1/31/12	RC	0	0	No
007	Exercise	Musculo/ Skeletal	Soreness	M	Month 6	2/25/2012	2/25/2012	2/26/2012	RC	3	0	No
007	Exercise	Constitutional	Fatigue	M	Month 6	2/25/2012	2/25/2012	2/26/2012	RC	3	0	No
007	Exercise	Musculo/Skeletal	Leg Fatigue/ Weakness	M	Month 7	3/5/2012	3/1/2012	3/4/2012	RC	2	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
007	Exercise	Musculo/ skeletal	Fall	M	Month 7	3/13/2012	3/11/2012	3/11/2012	RC	1	0	No
007	Exercise	Musculo/Skeletal	Fall	M	Month 7	3/23/2012	3/14/2012	3/14/2012	RC	1	0	No
008	Control	Musculo/ skeletal	Fall	M	TC week 6	3/9/2012	3/1/2012	3/1/2012	RC	0	0	No
008	Control	Musculo/ skeletal	Fall	M	TC week 11	4/18/2012	3/29/2012	3/29/2012	RC	0	0	No
009	Pre-Assignment	Constitutional	Fatigue	M	TC Week 1	1/10/2012	1/6/2012	1/9/2012	RC	2	0	No
009	Pre-Assignment	Musculo/ Skeletal	Fall	O	TC Week 2	1/15/2012	1/15/2012	1/17/2012	RC	0	1	No
009	Pre-Assignment	Musculo/ Skeletal	Fall	M	Month 1	2/17/2012	2/5/2012	2/10/2012	RC	0	0	No
009	Exercise	Musculo/ skeletal	® forearm soreness	M	TC Week 11	3/15/2012	3/9/2012	3/19/2012	RC	2	0	No
009	Exercise	Musculo/ Skeletal	® anterior tib cramp, soreness	O	TC Week 12	3/23/2012	3/17/2012	3/26/2012	RC	1	1	No
009	Exercise	Musculo/ Skeletal	Fall	M	email Week 13	3/26/2012	3/26/2012	3/26/2012	RC	0	0	No
010	Pre-Assignment	Musculo/ Skeletal	Fall	M	Month 1	2/15/2012	2/12/2012	2/13/2012	RC	0	0	No
010	Control	Upper Resp.	Viral illness – URI	O	TC week 8	3/15/2012	3/11/2012	3/15/2012	RC	0	1	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
010	Musculo/ Skeletal	Musculo/ skeletal	Fall	M	TC week 8	3/15/2012	3/8/2012	3/8/2012	RC	0	0	No

1 Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
2 Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
3 PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
4 Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

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Vice Chair and Residency Program Director in Rehabilitation Medicine

March 7, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on February 28, 2011. This report contained adverse events for subjects 001 and 002 reported from study initiation through and including February 27, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

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April 4, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on April 1, 2011. This report contained adverse events for subjects 001, 002 and 003 reported from study initiation through and including March 31, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E. Strauss, MD

Jackie (VIVO HC) FAX (212) 342-1263

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Vice Chair and Residency Program Director in Rehabilitation Medicine

May 6, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on May 2, 2011. This report contained adverse events for subjects 001, 002, 003, and 004 reported from study initiation through and including April 29, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

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Vice Chair and Residency Program Director in Rehabilitation Medicine

June 6, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on June 3, 2011. This report contained adverse events for subjects 001, 002, 003, 004, and 005 reported from study initiation through and including May 31, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E. Strauss MD

Nancy E. Strauss, MD

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Vice Chair and Residency Program Director in Rehabilitation Medicine

July 6, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on July 5, 2011. This report contained adverse events for subjects 001, 002, 003, 004, and 005 reported from study initiation through and including June 30, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E. Strauss MD

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Nancy E. Strauss, M.D.
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Vice Chair and Residency Program Director in Rehabilitation Medicine

August 1, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on August 1, 2011. This report contained adverse events for subjects 001, 002, 003, 004, and 005 reported from study initiation through and including July 29, 2011. There have been no adverse events reported to date for subject 006.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

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Nancy E. Strauss, M.D.
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September 22, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on September 7, 2011. This report contained adverse events for subjects 001, 002, 003, 004, and 005 reported from study initiation through and including August 31, 2011. There have been no adverse events reported to date for subjects 006 or 007.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

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Vice Chair and Residency Program Director in Rehabilitation Medicine

November 9, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on November 4, 2011. This report contained adverse events for subjects 001, 002, 003, 004, 005, and 007 reported from study initiation through and including October 31, 2011. There have been no adverse events reported to date for subject 006.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

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Nancy E. Strauss, M.D.
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October 5, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on October 3, 2011. This report contained adverse events for subjects 001, 002, 003, 004, and 005 reported from study initiation through and including September 30, 2011. There have been no adverse events reported to date for subjects 006 or 007.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

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Nancy E. Strauss, M.D.
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December 6, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on December 5, 2011. This report contained adverse events for subjects 001, 002, 003, 004, 005, and 007 reported from study initiation through and including November 30, 2011. There have been no adverse events reported to date for subject 006.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

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Nancy E. Strauss, M.D.
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January 9, 2012

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on January 9, 2012. This report contained adverse events for subjects 001, 002, 003, 004, 005, 006, and 007 reported from study initiation through and including January 4, 2012.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

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February 3, 2012

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on February 3, 2012. This report contained adverse events for subjects 001, 002, 003, 004, 005, 006, 007, and 009 reported from study initiation through and including February 1, 2012.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

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March 8, 2012

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on February 3, 2012. This report contained adverse events for subjects 001, 002, 003, 004, 005, 006, 007, 009, and 010 reported from study initiation through and including March 4, 2012.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

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April 2, 2012

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on April 2, 2012. This report contained adverse events for all 10 subjects reported from study initiation through and including March 30, 2012.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

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Nancy E. Strauss, M.D.
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May 3, 2012

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on April 2, 2012. This report contained adverse events for all 10 subjects reported from study initiation through and including April 30, 2012.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

Falls and Spinal Muscular Atrophy (SMA): Exploring Cause and Prevention

Montes J, McIsaac T, Dunaway S, Kamil-Rosenberg S, Sproule D, Garber C, De Vivo DC, Rao AK

Objective

To characterize falls by ambulatory SMA patients and possible association between falls and disturbed walking performance.

Background

Falls can lead to injury and compromise function of patients with neuromuscular disorders. Weakness is an obvious contributing factor. Gait variability is associated with falls in other neurological disorders and may be in SMA patients. Fatigue has been well documented in SMA, but an association between fatigue and falls has never been investigated.

Design/ Methods

Seven ambulatory patients with SMA completed a falls history questionnaire with information on 2 serious falls over a year. All subjects completed the 6MWT and quantitative gait analysis. We analyzed velocity, stride-length, stride-width, stride-time, swing-time, stance-time and coefficient of variation for gait measures. Strength and function measures also were assessed.

Fatigue was measured by the percent difference in gait velocity between the first and last passes over the gait mat during the 6MWT. Pearson correlation coefficients were used to examine association between gait, 6MWT variables and falls.

Results

All 7 subjects (age range= 10-48 years) reported falls in the past year (mean 18; range 1–42). Most falls occurred indoors while walking and were associated with factors including weakness, loss of balance, and tripping. Bruise and sprains were the most common injury. Stride-length variability was associated with falls ($r=0.793$; $p=0.033$). Other gait measures were not significantly correlated with falls. The number of falls was not associated with fatigue ($r=0.202$; $p=0.665$), 6MWT distance ($r=-0.000$; $p= .999$) or strength ($r = -0.126$; $p = 0.788$)

Discussion

Stride-length variability was associated with falls in SMA and may be related to selective weakness in hip flexor and knee extensor muscles. Future studies with larger samples are planned to examine the causal relationship between gait disturbances and falls. These studies anticipate rehabilitative interventions targeting factors that put this vulnerable population at risk for injury-causing falls.

Title: Leg Strength Predicts Dysfunction and Fatigue in Ambulatory Spinal Muscular Atrophy (SMA)

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Background
Fatigue is a prominent symptom in SMA type 3. The Six Minute Walk Test (6MWT) is a reliable clinical measure of fatigue. Mean power frequency (MPF) and root mean square amplitude (RMS) are electromyographic (EMG) measures that are physiological markers of fatigue. Incorporating EMG measures into the 6MWT should provide a real time evaluation of specific muscle groups responsible for fatigue-related changes. Since fiber type proportion is determined by its innervation, evaluating muscle fiber output provides down-stream information about the integrity of the motor neuron.

Objective
To determine the association between muscle weakness, muscle function, and fatigue.

Methods
A cross-sectional study of 10 ambulatory SMA patients (age range 10 – 49) was conducted. Participants performed the 6MWT with gait analysis and surface EMG from 4 muscles groups in the right leg. Average MPF and RMS amplitude was calculated from the EMG signal from each muscle, and stride length and velocity from gait analysis during corresponding strides in the first and last minutes. Strength measures were also collected. Repeated measures ANOVA was performed for all measures to examine changes in selected muscle groups during the first and last minutes of the 6MWT. Associations between RMS amplitude and MPF were analyzed using Spearman correlation coefficients. Regression analyses were performed to examine if muscle strength was predictive of fatigue.

Results
The mean 6MWT distance was 273.4 meters (range 53 – 492). Weakness of the hip flexors and extensors was greater than knee extensors and flexors and ankle muscles. Repeated measures ANOVA demonstrated a significant effect of trial (first and last minute during the 6MWT) for RMS Amplitude ($p = 0.038$), stride length ($p < 0.001$), and velocity ($p < 0.001$), but no effect for MPF ($p = 0.603$). There was a strong inverse relationship between RMS and MPF ($R = -0.72$; $p < 0.001$). Regression analysis showed that increased ankle plantar flexor strength was predictive of decrease in percent change in stride length ($F=18.356$, $p = 0.002$) and RMS amplitude ($F=12.217$, $p = 0.008$) over the 6MWT. Total leg strength was predictive of velocity ($F=9.406$, $p = 0.015$) as well as 6MWT distance ($F=9.314$, $p = 0.016$).

Discussion
The 6MWT describes motor fatigue in ambulatory SMA patients that can be quantified using gait and EMG measures. Weakness of ankle plantar flexors correlated with these fatigue-related changes and aggregate leg strength correlated with performance on the 6MWT. MPF is a sensitive measure of muscle fatigue but may not be informative in SMA. The inverse relationship of MPF to RMS amplitude may be reflective of the SMA muscle pathophysiology dictated by the diseased motor neuron. The surviving muscles have more viable hypertrophied type 1 motor units possibly resulting in a lower MPF. Our findings suggest that rehabilitation strategies should be focused on overall leg strength with the emphasis on the gastrocnemius muscle.

Acknowledgements
This study is supported by the Department of Defense; USAMRAA Grant/Cooperative award number: 09131005(W81XWH-10-1-0127) and the SMA Foundation.

Spinal Muscular Atrophy (SMA): An Asymmetric Disease by Patient Report

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BACKGROUND: SMA is characterized clinically as a symmetrical motor neuron disease. However; patients very often report that one side is significantly stronger; challenging the long standing assertion that SMA is a symmetrical disease. Little research has commented on this observation of asymmetry. Some published literature describes the proximal muscle weakness as largely symmetrical, and only rarely as one side being more affected than the other. We challenged our standard validated outcome measures of strength, function, and electrophysiology to determine if the patients' observations of asymmetry could be captured. The purpose of this study is to assess signs of asymmetry in ambulatory patients with SMA.

DESIGN/METHODS: Twelve ambulatory SMA participants performed the 6-minute walk test (6MWT) with quantitative gait analysis, manual muscle testing (MMT), hand-held dynamometry (HHD), Hammersmith Functional Motor Scale Expanded (HFMSE), and bilateral motor unit number estimation (MUNE) of the ulnar nerve. Gait parameters included step time, step length, swing percent of cycle, swing time, stance percent of cycle, and stance time. Paired samples t-tests were performed for each bilateral lower extremity variable, bilateral MUNE, and max ulnar compound motor action potential (CMAP) negative peak amplitude.

RESULTS: We found a significant electrophysiological difference between right and left ulnar nerves (MUNE $p = 0.050$, CMAP $p = 0.048$). There was no significant difference between right and left for strength or function measures (MMT $p = 0.526$, HHD knee flexion $p = 0.223$, HHD knee extension $p = 0.685$, and HFMSE $p = 1.00$). Temporal and spatial gait parameters for the first pass were not significantly different (p values ranged 0.117 – 0.407). Fatigue did not impact the last pass (p values ranged 0.104 – 0.975) or percent change (p values ranged 0.151 – 0.690) for any gait variables.

CONCLUSIONS: Electrophysiological measures including MUNE and CMAP did detect asymmetry in SMA. However, clinical outcome measures used to assess ambulatory patients with SMA did not detect asymmetry. Our ability to confirm these observations indicates that electrophysiological measures are more sensitive and specific than clinical outcome measures in documenting asymmetry of this bilateral disease. These findings likely reflect clinical outcome test insensitivity when assessing observations of asymmetry. Furthermore, asymmetry may be more difficult to detect in the milder phenotypes of SMA, demanding further study in more severe phenotypes. Patient confirmation of strength asymmetry may provide important insights into complications such as scoliosis.

Acknowledgements: This study is supported by the Department of Defense; USAMRAA Grant/Cooperative award number: 09131005(W81XWH-10-1-0127) and the SMA Foundation.

Performance of the Timed "Up & Go" Test (TUG) in Spinal Muscular Atrophy (SMA)

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BACKGROUND: The TUG is a quick, meaningful, and applied objective measure of balance and functional mobility. In adult motor neuron disease, TUG scores are associated with standard functional and strength assessments, decline linearly over time, and predict falls. It is a sensitive and reliable measure in inherited neuromuscular disorders and in children with physical disabilities, and warrants further investigation for use in ambulatory patients with SMA. The reliability and validity of the TUG have not been tested previously for patients with SMA. The purpose of this study is to assess test-retest reliability and validity for the TUG.

DESIGN/METHODS: Ten ambulatory patients with SMA (mean age 33 years, range 10 to 49 years;7 males) performed the TUG, 6-minute walk test (6MWT), timed 10 meter walk/run, manual muscle testing (MMT), hand-held dynamometry (HHD), Hammersmith Functional Motor Scale Expanded (HFMSE), and forced vital capacity (FVC) while participating in an exercise study. Test-retest reliability was assessed using data from the baseline and month 1 visits, prior to intervention. This was quantified by intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) using a one-way random effects analysis of variance model. Associations between the TUG and other outcomes to test convergent validity were analyzed using Pearson correlation coefficients ($p < .05$).

RESULTS: Mean TUG score for the participants was 15.81 sec (SD 10.74 sec, range 5.27 - 41.11 sec). Test-retest reliability was excellent for all participants (ICC: 0.945; 95% CI: 0.809–0.986). The TUG was significantly associated with MMT ($r = -0.796$, $p = 0.006$), knee flexion HHD ($r = -0.675$, $p = 0.032$), HFMSE score ($r = -0.655$, $p = 0.040$), and 10-m walk/run time ($r = 0.645$, $p = 0.044$). The associations with 6MWT ($r = -.482$, $p = 0.158$), knee extension HHD ($r = -0.381$, $p = 0.277$), and FVC ($r = -0.119$, $p = 0.744$) were not significant.

CONCLUSIONS: The TUG is a safe and reliable outcome measure for ambulatory patients with SMA and correlates with established standardized outcome measures for SMA. With additional research, the TUG is potentially useful in SMA as an outcome measure in intervention studies, a measure of change in functional mobility over time, and a measure of disability. The TUG adds value as a valid outcome measure for clinical trials in ambulatory subjects with SMA.

Acknowledgements: This study is supported by the Department of Defense; USAMRAA Grant/Cooperative award number: 09131005(W81XWH-10-1-0127) and the SMA Foundation.